

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
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ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 16 June 1999 (16.06.99)	
<b>International application No.</b> PCT/US98/20887	<b>Applicant's or agent's file reference</b> 31856-PCT
<b>International filing date</b> (day/month/year) 02 October 1998 (02.10.98)	<b>Priority date</b> (day/month/year) 03 October 1997 (03.10.97)
<b>Applicant</b> ITESCU, Silviu	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

16 April 1999 (16.04.99)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer R. Forax</p> <p>Telephone No.: (41-22) 338.83.38</p>
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**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C12Q 1/04, G01N 33/50</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/18231</b> <b>(43) International Publication Date:</b> 15 April 1999 (15.04.99)
<b>(21) International Application Number:</b> PCT/US98/20887 <b>(22) International Filing Date:</b> 2 October 1998 (02.10.98)  <b>(30) Priority Data:</b> 60/060,992 3 October 1997 (03.10.97) US 60/090,153 22 June 1998 (22.06.98) US  <b>(71) Applicant (for all designated States except US):</b> THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK [US/US]; 116th Street and Broadway, New York, NY 10027 (US).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> ITESCU, Silviu [AU/US]; Apartment 12E, 279 E. 44th Street, New York, NY 10017 (US).  <b>(74) Agents:</b> TANG, Henry et al.; Baker & Botts, LLP, 30 Rockefeller Plaza, New York, NY 10112-0228 (US).		<b>(81) Designated States:</b> AU, CA, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> METHOD FOR PREDICTING TRANSPLANT REJECTION  <b>(57) Abstract</b>  The present invention relates to a method for predicting whether or not transplant recipients are likely to reject tissue allografts. It is based, at least in part, on the discovery that, based on analysis of three immunologic factors, cardiac transplant recipients could be classified into risk categories for progression to high-grade rejection. The present invention, by enabling a determination of the risk for high-risk rejection in a transplant patient, reduces unnecessary diagnostic and therapeutic procedures in low risk patients and clinical intervention in patients who would most benefit.		

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/20887**A. CLASSIFICATION OF SUBJECT MATTER**IPC(5) : C12Q 1/04; G01N 33/50  
US CL : 435/7.24, 34

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.24, 34

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Database PREV 199800363183, ITESCU et al. 'An immunological algorithm to predict risk of high-grade rejection in cardiac transplant recipients.' In: Lancet (North American Edition), 25 July 1998, Volume 352, No. 9124, pages 263-270, see abstract.	1-7,19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

29 DECEMBER 1998

Date of mailing of the international search report

29 JAN 1999

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DAVID SAUNDERS

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/20887

### B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

Biosis

(transplant? or allograft? or graft?)(3a)reject? and HLA(w)DR# and IGG

### BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-7 and 19, drawn to assessing the risk of transplantation rejection via detection of activated T-cells and IgG anti HLA Class II antibodies.

Group II, claim(s) 8-9 and 13-16, drawn to kits containing solid phase HLA Class II antigens and reagent for detecting IgG.

Group III, claim(s) 10-11, drawn to kits containing complement and a denaturing agent.

Group IV, claim 12, drawn to kits containing cells and labeled anti-IgG.

Group V, claims 17-18, drawn to methods of detecting and comparing anti-HLA antibody reactivity against B-cells versus T-cells.

The inventions listed as Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The testing methods of Groups I and V involve different steps (e.g. only Group II requires the determining of the ratio of anti-HLA reactivity to B-cells versus T-cells), involve use of different reagents (e.g. only Group II requires the use of DTT), and can be conducted in different patients (e.g. the method of Group II can be conducted upon patients other than transplant patients, for example, multiply transfused patients or multiparous women). These methods therefore do not have the same special technical feature to provide for unity of invention.

The components of the kits of Groups II-IV bear no clear relationship to the methods of Groups I and II, and thus do not provide for a single inventive concept. For example, the kits of Groups II and IV require the provision of a means for detecting IgG antibody or a labeled anti-IgG antibody, but the use of such a reagent is not recited in the methods of Groups I or V. The kit of Group III requires providing complement and a denaturing agent; the method of Group I does not require the use of a denaturing agent, and the method of Group V does not require the use of complement. Furthermore, even if it were considered that there is a nexus between the kits of Groups II-IV and each of the methods of Groups I and V, it is to be noted that if multiple products, processes of manufacture, or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention of the claims (PCT article 17(3)(a)). Therefore, at most, applicant could only consider the first recited method and first recited kit as constituting the main invention.

Furthermore the kits of Groups II-IV would have uses in methods other than those of Groups I and V. For example, they could be used in HLA typing to determine HLA autoimmune disease associations. The kit of Group III could be used to conduct a complement fixation assay or a Jerne plaque assay. In any case, the components of the kits of Groups II-IV are all old and known for use in HLA typing, in complement fixation assays, and in Jerne plaque assays. The kits do not therefore constitute a contribution by applicant over the prior art and thus cannot be considered as involving an inventive concept under PCT Rule 13.1.

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 05 JUL 1999

WIPO PCT


REC'D 05 JUL 1999

WIPO PCT

Applicant's or agent's file reference 31856-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/20887	International filing date (day/month/year) 02 OCTOBER 1998	Priority date (day/month/year) 03 OCTOBER 1997
International Patent Classification (IPC) or national classification and IPC IPC(6): C12Q 1/04; G01N 33/50 and US Cl.: 435/7.24, 34		
Applicant THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 4 sheets.  
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
These annexes consist of a total of 0 sheets.

- This report contains indications relating to the following items:
  - ☒ Basis of the report
  - ☐ Priority
  - ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability
  - ☐ Lack of unity of invention
  - ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - ☐ Certain documents cited
  - ☐ Certain defects in the international application
  - ☐ Certain observations on the international application

Date of submission of the demand 16 APRIL 1999	Date of completion of this report 04 JUNE 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DAVID SAUNDERS Telephone No. (703) 308-0196 JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX 

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/20887

**I. Basis of the report**

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

☒ the international application as originally filed.

☒ the description, pages 1-42 , as originally filed.

pages NONE , filed with the demand.

pages NONE , filed with the letter of \_\_\_\_\_.

pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

☒ the claims, Nos. 1-19 , as originally filed.

Nos. NONE , as amended under Article 19.

Nos. NONE , filed with the demand.

Nos. NONE , filed with the letter of \_\_\_\_\_.

Nos. \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

☒ the drawings, sheets/fig 1-8 , as originally filed.

sheets/fig NONE , filed with the demand.

sheets/fig NONE , filed with the letter of \_\_\_\_\_.

sheets/fig \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE .

☒ the claims, Nos. NONE .

☒ the drawings, sheets/fig NONE .

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.  
PCT/US98/20887**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 8-18

because:

☐ the said international application, or the said claim Nos. \_ relate to the following subject matter which does not require international preliminary examination (*specify*).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_ are so unclear that no meaningful opinion could be formed (*specify*).

☐ the claims, or said claims Nos. \_ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 8-18.



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/20887

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1-7,19</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>1-7,19</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>1-7,19</u>	YES
	Claims <u>NONE</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1-7 and 19 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the instantly claimed method which determines IgG anti HLA-DR as an indicator of transplant rejection. The article of ITESCU ET AL, cited in the search report was published after applicant's priority dates. The invention has industrial applicability by virtue of aiding in the identification of transplant recipients that are likely to reject transplanted organs.

\_\_\_\_\_ NEW CITATIONS \_\_\_\_\_  
NONE